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Review

Ca^{2+} sources for the exocytotic release of glutamate from astrocytes ☆

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ABSTRACT

Astrocytes can exocytotically release the gliotransmitter glutamate from vesicular compartments. Increased cytosolic Ca^{2+} concentration is necessary and sufficient for this process. The predominant source of Ca^{2+} for exocytosis in astrocytes resides within the endoplasmic reticulum (ER). Inositol 1,4,5-trisphosphate and ryanodine receptors of the ER provide a conduit for the release of Ca^{2+} to the cytosol. The ER store is (re)filled by the store-specific Ca^{2+}-ATPase. Ultimately, the depleted ER is replenished by Ca^{2+} which enters from the extracellular space to the cytosol via store-operated Ca^{2+} entry; the TRPC1 protein has been implicated in this part of the astrocytic exocytotic process. Voltage-gated Ca^{2+} channels and plasma membrane Na^{+}/Ca^{2+} exchangers are additional means for cytosolic Ca^{2+} entry. Cytosolic Ca^{2+} levels can be modulated by mitochondria, which can take up cytosolic Ca^{2+} via the Ca^{2+} uniporter and release Ca^{2+} into cytosol via the mitochondrial Na^{+}/Ca^{2+} exchanger, as well as by the formation of the mitochondrial permeability transition pore. The interplay between various Ca^{2+} sources generates cytosolic Ca^{2+} dynamics that can drive Ca^{2+}-dependent exocytotic release of glutamate from astrocytes. An understanding of this process in vivo will reveal some of the astrocytic functions in health and disease of the brain. This article is part of a Special Issue entitled: 11th European Symposium on Calcium.

1. Introduction

Functional connectivity of the neural networks is fundamental for information flow and information processing in the nervous system. The mechanisms, which underlie this connectivity, are omnipresent and evolutionary conserved. These mechanisms are represented by (i) several sets of plasmalemmal and intracellular ion channels, receptors and transporters, capable of redistributing ions between cellular compartments and triggering intracellular enzymatic reactions and (ii) by specialized vesicles able to concentrate transmitter molecules and release them upon appropriate stimulation. The coupling of membrane excitation and release of transmitters is chiefly controlled by a Ca^{2+} signaling system that is expressed in virtually every cell throughout the evolution [1,2]. The Ca^{2+} signaling system involves a group of relatively few specific molecular component types that build up Ca^{2+} concentration gradients between cellular compartments and provide for rapid Ca^{2+} diffusion, driven by these gradients, in response to physiological stimulation [3–9]. At the receiving end of the Ca^{2+} signaling system, numerous "Ca^{2+} sensors" represented by Ca^{2+}-sensitive proteins execute cellular responses. Different affinities of Ca^{2+} sensors to Ca^{2+} determine the specificity of signaling (see e.g., refs. [10–14]). As far as exocytotic release of transmitters is concerned, several Ca^{2+}-sensitive synaptotagmins are implicated as a trigger for the process of vesicle merger with the plasma membrane that culminates in the release of vesicular content (reviewed in refs. [15,16]).

The soluble *N*-ethyl maleimide-sensitive fusion protein (NSF) attachment protein (SNAP) receptor (SNARE) complex [17] is ubiquitously employed for membrane fusion in organisms ranging from yeast to human [18]. Two major neural cell types, neurons and astrocytes, use regulated exocytosis for their intercellular communication [19]. The molecular machinery necessary for regulated exocytosis includes the core ternary SNARE complex comprised of the vesicle-associated membrane protein synaptobrevin 2 and proteins located at the plasma membrane: syntaxin and synaptosome-associated protein of 25 kDa (SNAP25) in neurons; in astroglia the homologue of the latter, SNAP23, is employed (reviewed in refs. [20–22]). This complex is assisted by a plethora of associated proteins, most notably the Ca^{2+} sensor synaptotagmin 1 in neurons (reviewed in ref. [23]) and its homologue synaptotagmin 4 in astrocytes [24]. The expression of mutated synaptotagmin 4 exhibited a dominant-negative effect by reducing Ca^{2+}-dependent glutamate release from astrocytes [24]. However, synaptotagmin 4 lacks Ca^{2+}-binding properties [25], thereby leaving the identity of a Ca^{2+} sensor for regulated exocytosis in astrocytes elusive. The uptake of glutamate into vesicles is carried out by vesicle

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membrane bound proteins, the vesicular glutamate transporters (VGLUTs), which transport glutamate into vesicles using the proton concentration gradient established across the vesicular membrane by another vesicular membrane protein, vacuolar type H^+-ATPase (V-ATPase). While it is widely accepted that neurons express these proteins [26], only recently it has been demonstrated that astrocytes express all the three isoforms of VGLUTs (1, 2, 3) as well as V-ATPase [27–32]. Perhaps due to protein stability of VGLUTs [33] consensus cannot be reached on the presence of their message [34].

In the nervous system transmitter molecules are released from two cellular populations, from neurons and from neuroglia. Neurotransmitters are generally released from neurons at specialized structures known as presynaptic terminals, whereas gliotransmitters are secreted by astrocytes without apparent spatial restrictions. Furthermore, the mechanisms providing Ca^{2+} for initiation of exocytosis in neurons vs. glia are fundamentally different. In neurons microdomains of high Ca^{2+} concentration that drive exocytosis, arise exclusively from rapid Ca^{2+} entry through voltage-gated plasmalemmal Ca^{2+} channels [35,36], whereas in astrocytes Ca^{2+} is delivered from both intracellular and extracellular sources [37]. In this essay we shall overview the main pathways of Ca^{2+} delivery within astrocytes and discuss the relevance of these pathways for exocytotic release of the gliotransmitter glutamate.

2. Glial calcium excitability

Calcium signaling is specifically important for glial physiology. It is generally considered that all types of electrically non-excitable glia, that is astrocytes, oligodendrocytes, ependymal cells and microglia, which are not capable of generating action potentials despite the presence of voltage-gated ion channels (reviewed in [38]), utilize a Ca^{2+} signaling system as a substrate for their excitability [39–41]. Indeed, initial experiments on cultured glial cells identified the expression of multiple metabotropic receptors that, when activated by physiological ligands, triggered production of inositol 1,4,5-trisphosphate ($InsP_3$) and subsequent $InsP_3$-induced Ca^{2+} release from the endoplasmic reticulum (ER) Ca^{2+} store [42,43]. The $InsP_3$-induced Ca^{2+} release is indispensable for initiation and maintenance of glial intercellular Ca^{2+} waves that provide for long-range signaling [44,45]. These initial in vitro observations were subsequently confirmed in experiments in situ and in vivo, which demonstrated that stimulation of glial metabotropic receptors triggers cytosolic Ca^{2+} signals and propagating intercellular Ca^{2+} waves [46–50]. The current hypothesis of glial Ca^{2+} excitability therefore regards the endomembrane that forms the ER, as an excitable medium and $InsP_3$ receptors ($InsP_3Rs$) as primary molecules that initiate Ca^{2+} release following physiological stimulation. Initial Ca^{2+} release is subsequently amplified by Ca^{2+}-dependent recruitment of ER Ca^{2+} channels, the $InsP_3Rs$ and ryanodine receptors (RyRs), thus triggering propagating glial Ca^{2+} signals. It should be noted that both $InsP_3Rs$ and RyRs can be activated by an increase in cytosolic/intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$), a process referred to as the Ca^{2+}-induced Ca^{2+} release (CICR). The preeminence of intracellular Ca^{2+} as the source in glial signaling, however, does not exclude a role for plasmalemmal pathways for Ca^{2+} entry in shaping Ca^{2+} signals.

3. Intracellular sources: ER and mitochondria

3.1. ER Ca^{2+} store: $InsP_3$- and Ca^{2+}-induced Ca^{2+} release

The ER represents a dynamic network of tubules and cisternae distributed throughout the eukaryotic cell [51,52]. In neural cells the ER is distributed throughout the cell body, forms the nuclear envelope and extends towards most distal processes [51,52]. The ER performs many functions being the place for protein synthesis and protein post-translational folding as well as providing for intracellular transport of various substances [52–54]. The ER is also a signaling organelle, which integrates various extra- and intracellular signals and generates its own signals that control overall biosynthetic activity and adaptive cell responses [55,56]. The ER acts as a dynamic Ca^{2+} store that generates and shapes cytosolic Ca^{2+} signals. As the Ca^{2+} store, the ER has its own Ca^{2+} homeostatic machinery, based around sarco(endo)plasmic reticulum Ca^{2+} ATPases (SERCAs) that transport Ca^{2+} into the ER lumen against the concentration gradient and oppose leakage from the ER stores [57]. Because of this pumping activity the ER is able to accumulate large amounts of Ca^{2+}, which, in association with low Ca^{2+} affinity of ER Ca^{2+} binding proteins (typical K_D ~ 0.5–1 mM), determines a high concentration of intra-ER free Ca^{2+} (intraluminal free Ca^{2+} concentration, $[Ca^{2+}]_L$, range 0.2–1.0 mM [58–63]) and attains a steep Ca^{2+} concentration gradient between the ER lumen and the cytosol. Physiological stimulation opens specific intracellular Ca^{2+} channels, the $InsP_3Rs$ and RyRs, and perhaps some other types of ER Ca^{2+} channels [64–66]), localized in the endomembrane. Influx of Ca^{2+} from the ER to the cytosol, the process generally termed as Ca^{2+} release, produces cytosolic Ca^{2+} concentration ($[Ca^{2+}]_i$) transients which globally average low- to mid-micromolar range. However, much higher levels of $[Ca^{2+}]_i$ (10 to ~ 100 μM) can be reached in restricted subcellular regions, located in the vicinity of Ca^{2+} entry sites, for example around the inner mouth of $InsP_3Rs$ [67].

Importantly, $[Ca^{2+}]_L$ fluctuations arising from Ca^{2+} release also act as a signaling events inside the ER by changing the activity of intra-ER enzymes such as chaperones [68]. The activity of Ca^{2+} release channels and of the SERCA pumps is tightly controlled by both $InsP_3$ and $[Ca^{2+}]_L$ which safeguards ER Ca^{2+} homeostasis [69]. Another important factor of ER Ca^{2+} homeostasis is the internal continuity of the ER that facilitates intraluminal Ca^{2+} diffusion and prevents local Ca^{2+} depletion [70–72].

The majority of metabotropic neurotransmitter receptors expressed in neuroglia activate the phopspholipase C/$InsP_3$ signaling cascade that results in the opening of $InsP_3Rs$ and $InsP_3$-induced Ca^{2+} release [6,73,74]. Although all three types of $InsP_3Rs$ are expressed in neuroglia at the mRNA level [75–77] the $InsP_3R$ type 2 seems to be the predominant isoform in astrocytes [78]. In the hippocampus, $InsP_3R$ 2 immunoreactivity displays a punctate staining at fine branches of astrocytic processes [79]. Functionally, $InsP_3$-induced Ca^{2+} release was demonstrated in all types of glial cells in vitro and in situ (see, e.g., refs. [39,41,43,46,47,80–82]). The role for RyRs in shaping Ca^{2+} release in neuroglia remains debatable; the contribution of RyR-mediated CICR was documented for oligodendrocytes in the spinal cord [83] and caffeine-induced Ca^{2+} release was found in astroglial cells in thalamus [84]. In contrast, the contribution of RyRs to hippocampal astrocyte Ca^{2+} signaling is negligible [57], a finding incongruent with the demonstration that astrocytes of the hippocampus express RyRs receptors at both the mRNA and protein levels [85,86]).

The importance of the ER Ca^{2+} release for gliotransmission was initially deduced from experiments on cultured cells which showed that inhibition of ER Ca^{2+} accumulation by thapsigargin, a specific SERCA blocker [87], almost completely eliminated Ca^{2+}-dependent glutamate release from astrocytes [88,89]. Detailed analysis of the contribution of $InsP_3Rs$ and RyRs to Ca^{2+}-dependent glutamate release from astrocytes was performed on cultured non-coupled astrocytes, thus excluding artifacts associated with the glial syncytium [90]. These experiments confirmed that the ER acted as a main source of Ca^{2+} for exocytotic gliotransmitter release, because exposure of astrocytes to thapsigargin substantially reduced (32% of control) mechanically induced glutamate release (Fig. 1). Subsequent experiments demonstrated that both $InsP_3R$-mediated and RyR-mediated Ca^{2+} release pathways were involved in Ca^{2+}-dependent glutamate release from astrocytes (Fig. 1). Hence, the exposure of astrocytes to diphenylboric acid 2-aminoethyl ester (2-APB; 75 μM; 10 min), a cell-permeable $InsP_3R$ antagonist [91], which can also block the store-operated Ca^{2+} entry [92,93], reduced the mechanically induced glutamate release (19% of

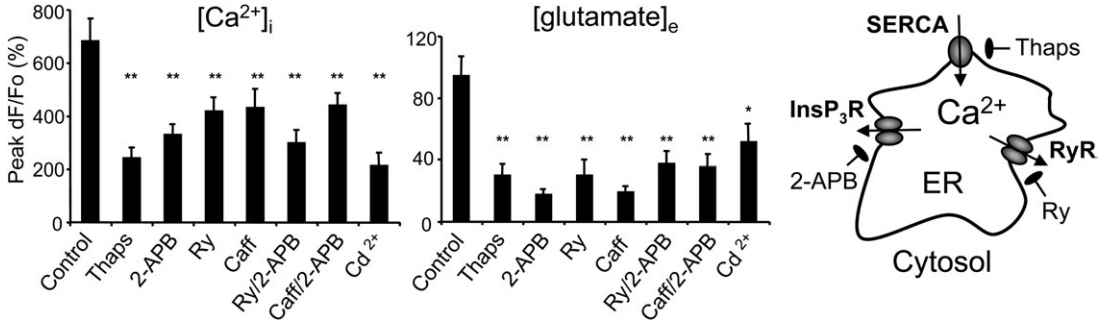

Fig. 1. The ER store is the predominant source of Ca^{2+} for Ca^{2+}-dependent glutamate release from astrocytes. Mechanically induced intracellular/cytosolic Ca^{2+} concentration ($[Ca^{2+}]_i$) increases and consequential glutamate release from astrocytes are reduced when thapsigargin (Thaps) blocks the activity of the store-specific sarco-endoplasmic reticulum Ca^{2+}-ATPase (SERCA) in these glial cells. Both $InsP_3$ and ryanodine (Ry) receptors ($InsP_3R$ and RyR) are conduits for the supply of cytosolic Ca^{2+} from the ER store. Diphenylboric acid 2-aminoethyl ester (2-APB), an $InsP_3R$ antagonist, reduced mechanically induced Ca^{2+} transients and glutamate release. Similar effects were observed when astrocytes were pre-incubated with either Ry to block RyRs or caffeine (Caff) to persistently simulate RyRs and deplete the ER store. The combined treatments, Ry/2-APB and Caff/2-APB, did not have any additive effect on reduction of Ca^{2+} accumulation and glutamate release. The presence of external Cd^{2+} caused the reduction of mechanically induced Ca^{2+} accumulation and glutamate release, implicating the role of the Ca^{2+}entry from the extracellular space in this process. Levels of cytosolic Ca^{2+} and extracellular glutamate ($[glutamate]_e$) were fluorescently monitored in parallel and represented as dF/Fo. Asterisks indicate significance ($^*p<0.05$, $^{**}p<0.01$). Modified from ref. [90]. A drawing (not to scale) of the ER depicts sites of pharmacological actions.

control). The pre-incubation of astrocytes with ryanodine (10 μM, 10 min) [94,95], at concentration which can block the release of Ca^{2+} from the ER via RyRs [96–98] decreased mechanically induced glutamate release (32% of control). Similarly, the pre-incubation of astrocytes with caffeine (10 mM, 10 min), which depletes the ER through persistent activation of RyRs, caused the reduction in glutamate release (21% of control). It should be noted that caffeine is also a potent blocker of $InsP_3Rs$ with $K_D \sim 1.6$ mM [99–101]. When astrocytes were pre-treated with combination of 2-APB with ryanodine or caffeine there was no additive effect on mechanically induced glutamate release when compared to treatments with one pharmacological agent only (Fig. 1). In agreement with the dual inhibitory action of 2-APB on the $InsP_3R$ and the store-operated Ca^{2+} entry, exposure of astrocytes to Cd^{2+} (100 μM, 1–10 min), a broad spectrum antagonist of Ca^{2+} entry through Ca^{2+} permeable plasma membrane channels, reduced mechanically induced glutamate release (55% of control). All the above pharmacological effects on the reduction of glutamate release where echoed by, in parallel, changes in the mechanically induced $[Ca^{2+}]_i$ transients (Fig. 1). Taken together, these data suggested that the predominant source of Ca^{2+} for mechanically induced exocytotic glutamate release from astrocytes originates from the ER with the Ca^{2+} delivery via both $InsP_3R$ and RyRs, while some Ca^{2+} influx from the extracellular space plays a role as well.

3.2. Mitochondria

Mitochondria represent the second class of organelles critically involved in cellular Ca^{2+} handling [102]. The mitochondrial role is complex and multifaceted. First, mitochondria have the ability to accumulate large amounts of cytosolic Ca^{2+} utilizing highly selective Ca^{2+} uniporters [103,104]. Second, mitochondria located in spatial proximity to the sites of Ca^{2+} entry (both at plasmalemmal and ER membrane) determine Ca^{2+} concentration in microdomains and regulate the function of Ca^{2+} channels [105–107]. The localization of mitochondria also determines spatio-temporal organization of cellular Ca^{2+} signals and mitochondrial "firewalls" act as powerful dynamic Ca^{2+} buffers that segregate Ca^{2+} signals between different cellular compartments [108,109]. In addition, mitochondrial Ca^{2+} uptake and release regulate $[Ca^{2+}]_i$ oscillations and propagating Ca^{2+} waves [110–113]. Calcium ions entering the mitochondria generate a specific type of intra-mitochondrial signaling that regulates energy production [114,115]. The latter is in turn crucial for maintaining ER Ca^{2+} homeostasis and store-operated Ca^{2+} entry [106]. In a sense mitochondria can be regarded as Ca^{2+} signaling dispatchers that coordinate different Ca^{2+} fluxes to form a specific Ca^{2+} signal.

By shaping astroglial Ca^{2+} signals mitochondria are directly involved in the regulation of exocytotic glutamate release. In cultured cortical astrocytes the role of mitochondrial buffering was pharmacologically assessed [116] (Fig. 2). Inhibition of mitochondrial Ca^{2+} uniporters with Ruthenium 360 increased mechanically induced $[Ca^{2+}]_i$ loads and potentiated the release of glutamate. Consistently, the inhibition of mitochondrial Ca^{2+} release, either by blocking the mitochondrial Na^+/Ca^{2+} exchanger with 7-chloro-5-(2-chlorophenyl)-1,5-dihydro-4,1-benzothiazepin-2(3 H)-one (CGP37157) or by inhibiting the mitochondrial permeability transition pore with cyclosporin A, reduced both the cytosolic Ca^{2+} loads and

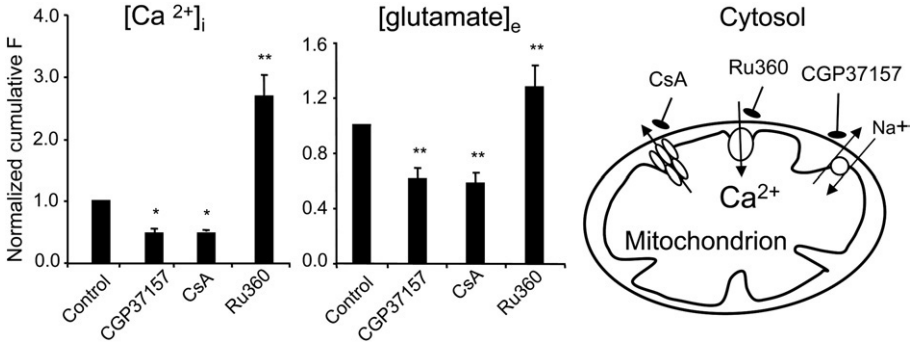

Fig. 2. Cytosolic Ca^{2+} handling in Ca^{2+}-dependent exocytotic glutamate release from astrocytes can be affected by mitochondria. Mitochondrial Ca^{2+} uptake is mediated by the uniporter which can be blocked by (Ru360), leading to increased $[Ca^{2+}]_i$ and glutamate release. The reduction in $[Ca^{2+}]_i$ and glutamate release is evident when the exit of Ca^{2+} from the mitochondrial matrix through either the Na^+/Ca^{2+} exchanger or the mitochondrial permeability transition pore is blocked by CGP37157 or cyclosporin A (CsA), respectively. Levels of $[Ca^{2+}]_i$ and $[glutamate]_e$ were fluorescently monitored in parallel and represented as normalized cumulative fluorescence (F). Asterisks indicate significance ($^*p<0.05$, $^{**}p<0.01$). Modified from ref. [37]. A drawing (not to scale) of the mitochondrion indicates sites of pharmacological actions.

consequential glutamate release (Fig. 2). Taken together, this study showed that mitochondria can buffer transient increases in cytosolic Ca^{2+} and consequently modulate Ca^{2+} -dependent exocytotic glutamate release from cultured astrocytes.

4. Extracellular sources: Channels and exchangers

4.1. Plasmalemmal voltage- and ligand-gated channels

4.1.1. Voltage-gated Ca^{2+} channels (VGCCs)

The first experimental evidence indicating possible functional expression of plasma membrane voltage-gated Ca^{2+} channels (VGCCs) were performed on glial fibrillary acidic protein (GFAP)-positive cultured (6–8 weeks in vitro) astrocytes pre-treated with a cell permeant dibutyryl form of cAMP (db-cAMP) for 2–8 h prior to recording [117]. The cells were current-clamped with microelectrodes. Voltage-gated Na^+ channels were inhibited by 1 μM tetrodotoxin, while the plasma membrane K^+ channel permeability was blocked by 5 mM tetraethylammonium cations. In such conditions and in the presence of 5–10 mM Ba^{2+} in the extracellular solution, glial cells exhibited slow plasma membrane depolarizing transients that were sensitive to Cd^{2+} and Mn^{2+}, indicating Ba^{2+} entry through VGCCs. Several years later, low- (T type) and high- (L type) threshold Ca^{2+} currents were recorded from voltage-clamped cultured astrocytes ([118–122], see also refs. [38,123] for review). Often some treatments of astroglia, such as incubation with db-cAMP, co-culturing with neurons, or acute oxidative stress, was required to reveal L type Ca^{2+} currents [120,121,124,125]. Rat cultured astrocytes were found to express specific mRNA encoding four main types of high-voltage-activated Ca^{2+} channels, namely α_{1A} (P/Q type), α_{1B} (N type), α_{1C} (L type), and α_{1E} (R type) subunits, although electrophysiological recordings (both whole-cell and single channel) detected only L- ($Ca_v1.2$), N- ($Ca_v2.2$), and R- ($Ca_v2.3$) type Ca^{2+} channels [126]. Western blot analysis detected expression of proteins for α_{1B}, α_{1C}, α_{1D}, α_{1E}, and α_{1G} (T type), but not α_{1A} (P/Q type), proteins in GFAP-positive cultured astrocytes [127]. The $[Ca^{2+}]_i$ recordings on cultured or freshly isolated astrocytes identified $[Ca^{2+}]_i$ transients sensitive to Ca^{2+} channel blockers thus indicating contribution of VGCCs in glial Ca^{2+} signaling [128–130].

Functional expression of VGCCs in astrocytes in situ is much less characterized. In acute slices from the visual cortex and the CA1 hippocampal region of developing rats, patch-clamp whole-cell recordings from astrocytes fail to detect any voltage-dependent Ca^{2+} currents [131]. However, immunoreactivity for $Ca_v2.2$ (N type) $Ca_v2.3$ (R type) subunits was detected in pituicytes (hypophyseal astrocytes) in situ, whereas deprivation of water for 24 h induced a significant increase in immunoreactivity of $Ca_v1.2$ (L type) [132]. There is also evidence indicating the up-regulation of expression of $Ca_v1.3$ or $Ca_v2.1$ channels in reactive hippocampal astrocytes at 1 week and 2 months after pilocarpine-induced status epilepticus [133]. Voltage–clamp experiments on glutamine synthetase-positive cells, probably immature astroglia, in hippocampus of 9- to 12-old-day mice demonstrated both low- and high-threshold Ca^{2+} currents [134]. Calcium influx, mediated by T and L type of VGCCs was also detected in astrocytes from neurogenic subventricular zone [135], while L type Ca^{2+} channels were reported to trigger Ca^{2+} oscillations in astroglia from the ventrobasal thalamus [84,136]. Nonetheless the data on functional expression of VGCCs in mature astrocytes in situ remain scarce, and their functional role questionable. There is also some evidence that Ca^{2+} may enter astrocytes through $K_{ir}4.1$ inward rectifier channels when extracellular K^+ concentration was lowered below 2 mM [137,138]; the actual mechanism of this Ca^{2+} entry through K^+ channels pathway remains somewhat puzzling.

As alluded to above, Parri et al. [136] showed that astrocytes in freshly prepared slices from ventrobasal thalamus of 5- to 17-day-old rats displayed intrinsic $[Ca^{2+}]_i$ oscillations which lead to glutamate release and consequential *N*-methy-D-aspartate (NMDA) receptor-mediated neuronal excitability. The oscillations required Ca^{2+} release from form the ER intracellular store since SERCA inhibitors thapsigargin and cyclopiazonic acid (CPA) blocked them. However, they also required Ca^{2+} entry from the extracellular space because they were inhibited by the dihydropyridine (DHP) antagonist nifedipine [136]. This finding implicated the involvement of L type VGCCs in astrocytic cytosolic Ca^{2+} dynamics. This was further supported by the effect of the DHP positive modulator BayK8644 in increasing the number of astrocytes displaying cytosolic Ca^{2+} oscillations [84]. Additionally, when the driving force for Ca^{2+} entry was increased by elevating extracellular Ca^{2+} concentration from 2.5 mM to 5 mM, there was an increased proportion of spontaneously active astrocytes as well as the increased frequency of cytosolic Ca^{2+} transients in individual astrocytes [84]. Although the effects of VGCC manipulations on glutamate release from astrocytes were not tested directly, it is tempting to speculate that these channels could be an additional conduit for Ca^{2+} supply for glutamate release from astrocytes. Recently, the experiments using cultured astrocytes from hippocampi of embryonic rats that were replated multiple times attempted to test the role of VGCCs in exocytotic release of glutamate from astroglia [139]. The depolarization of astrocytes with high extracellular K^+ (75 mM) triggered $[Ca^{2+}]_i$ elevation. This effect was abolished by the addition of extracellular Cd^{2+} or removal of Ca^{2+} from the extracellular medium. Depolarization-dependent $[Ca^{2+}]_i$ transients caused glutamate release, which was sensitive to extracellular Cd^{2+} and removal of extracellular Ca^{2+}, as well as to blockers of exocytosis. Cultured astrocytes used in this study expressed mRNA for α_{1B}, α_{1C}, α_{1D}, and α_{1E} subunits of VGCCs. These results implicate VGCCs as a conduit for delivery of extracellular Ca^{2+} to cytosol for regulated exocytosis of glutamate from embryonic astrocytes in prolonged culture.

4.1.2. Ligand-gated Ca^{2+} channels

Astrocytes in vitro and in situ express several types of Ca^{2+} permeable ionotropic receptors; many of which have appreciable Ca^{2+} permeability (see [38,140–142] for detailed overview). Two types of glutamate receptors, the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and NMDA receptors can provide a conduit for Ca^{2+} entry from the extracellular space into the cytosol of astroglial cells. The AMPA receptors expressed in Bergmann glia and in some astrocytes [143,144] are devoid of the GluR2 subunit and thus have some Ca^{2+} permeability ($P_{Ca}/P_{monovalent}$~1 [145]). The physiological contribution of AMPA receptors to Ca^{2+} signaling is however negligible because their rapid desensitization limits periods of Ca^{2+} entry to several tens of milliseconds. In contrast the NMDA receptors, expressed in astrocytes, can provide substantial Ca^{2+} entry because of much higher Ca^{2+} permeability and absence of desensitization [142,146,147]. Physiologically relevant Ca^{2+} influx can also be provided by P2X purinoreceptors expressed in cortical astroglia [148] and by nicotinic acetylcholine receptors (nAChRs). Functional nAChRs-mediated Ca^{2+} signaling was identified only in cultured astrocytes [149,150], which express α7 subunit responsible for high Ca^{2+} permeability. Activation of these receptors caused Ca^{2+} influx from the extracellular space, which triggered CICR from the ER. However, astrocytes in acute hippocampal slices appear only to express functional metabotropic AChs [151,152].

The role of ligand-gated ionotropic receptors in exocytotic glutamate release from astrocytes is speculative at the moment. Exposure of hippocampal astrocytes to AMPA did not induce glutamate release [28]. This is consistent with the expression of GluR2 subunit in hippocampal astrocytes which consequently display low Ca^{2+} permeability through their AMPA channels [28]. However, what is the role of Ca^{2+} permeable AMPA receptors on glutamate release in those astrocytes that express such receptors remains undetermined. Similarly, whether activation of astrocytic NMDA or other ionotropic receptors leading to increases in $[Ca^{2+}]_i$ would prompt Ca^{2+}-dependent exocytotic glutamate release remains unknown at the moment.

4.2. Store operated Ca^{2+} entry (SOCE): Role for transient receptor potential (TRP) channels

The store-operated Ca^{2+} entry (SOCE), activated following the depletion of the ER Ca^{2+} store, is generally present in all types of glial cells (see, e.g., refs. [153–156]). The molecular mechanism of SOCE in astroglia probably involves several molecular entities within their signaling cascades. The classical Ca^{2+}-release activated Ca^{2+} currents (I_{CRAC}) [157] have not been detected in astroglia; similarly there are no published data on the astrocyte expression of the STIM1/ORAI protein complex that forms CRAC channels [158].

The products of transient receptor potential (TRP) genes that have been implicated in SOCE have been indentified in astrocytes [159–162]. TRP activity plays a role in the regulation of astrocytic Ca^{2+} homeostasis. For instance, an antisense knock down of the canonical TRP 1 (TRPC1) gene [160] or an acute immunological treatment using blocking antibodies against the TRPC1 protein channel pore [162] significantly reduced SOCE in cultured astroglia. However, expression of TRPC1 alone does not commonly form homomeric channels [163]. Instead, TRPC1 is known to form functional heteromultimers with two other TRPC family proteins that are expressed in the brain, namely TRPC4 and TRPC5 [163–165]. Indeed, in addition to TRPC1 protein, astrocytes in cultured as well as freshly isolated astrocytes express TRPC4 and TRPC5 proteins [160,162]. Thus, tampering with the activity/expression of TRPC1 protein, one can affect the activity of the native heteromultimeric channel in attempt to define its role in supplying Ca^{2+} for exocytotic process in astrocytes. Malarkey et al. [162] employed this experimental paradigm by using an antibody directed at an epitope in the pore forming region of the TRPC1 protein expressed in cultured astrocytes. This blocking antibody reduced mechanically induced cytosolic Ca^{2+} elevations as well as the consequential glutamate release from astrocytes (Fig. 3), indicating that TRPC1 protein can play a functional role in exocytotic glutamate release from astrocytes.

4.3. Sodium–calcium exchanger (NCX)

The Na^+/Ca^{2+} exchangers, which in mammals are represented by three subtypes NCX1, NCX2 and NCX3, belong to Ca^{2+}/cation antiporter superfamily [166] and are important parts of the Ca^{2+} homeostatic/signaling machinery. All three types of NCX are expressed in astroglia and are primarily localized in perisynaptic processes, especially in those ensheathing excitatory synapses [167]. Astroglial NCXs are functionally active and NCX-mediated Ca^{2+} fluxes were found in both cultured astrocytes and astroglial cells in situ [168–171]. The NCX-dependent Ca^{2+} transport is important for shaping astroglial Ca^{2+} signals participating in both Ca^{2+} extrusion and Ca^{2+} delivery [171,172]. NCXs can operate in two modes, either in the forward mode responsible for the Ca^{2+} extrusion from the cytosol into the extracellular space or in the reverse mode providing for the Ca^{2+} entry from the extracellular space into the cytosol. The operation mode selection depends on the transmembrane Na^+ gradient and the plasma membrane potential. Both the increase in $[Na^+]_i$ and the membrane depolarization favor the reverse operation of the NCX [171]. Increases in $[Na^+]_i$ that accompany activation of astroglial ionotropic receptors and glutamate transporters can engage this exchanger in the reverse operation mode resulting in NCX-mediated $[Ca^{2+}]_i$ increases [173]. Similarly, mild depolarization, due to an increase in extracellular K^+ (15 and 35 mM), of astrocytes cultured from adult rats (70–90 days old) caused NCXs to operate in the reverse mode and generated $[Ca^{2+}]_i$ increases [174]. This effect was not associated with VGCCs because it was insensitive to VGCC blockers, but could be blocked by 2-[2-[4-(4-nitrobenzyloxy)phenyl] ethyl]isothiurea (KB-R7943) implicating the reverse mode of NCXs. The $[Ca^{2+}]_i$ increase caused by NCX triggered release of glutamate from astrocytes that was sensitive to KB-R7943 as well as to a blocker of exocytosis. Thus, the astrocytic NCXs can transport Ca^{2+} from the extracellular space into the cytosol to drive exocytosis in these glial cells, leading to the release of gliotrasmitter glutamate.

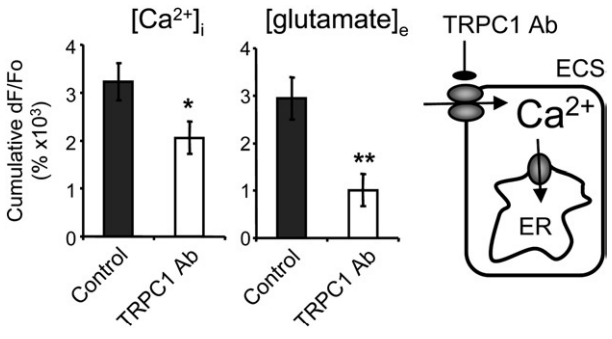

Fig. 3. TRPC1 containing channel plays a role in exocytotic glutamate release from astrocytes. Mechanically evoked cytosolic Ca^{2+} loads and consequential glutamate release from astrocytes are reduced in the presence of a blocking antibody against the TRPC1 channel pore. Levels of $[Ca^{2+}]_i$ and $[glutamate]_e$ were fluorescently monitored in parallel and represented as cumulative dF/Fo. Asterisks indicate significance ($^*p<0.05$, $^{**}p<0.01$). Modified from ref. [162]. A drawing (not to scale) of the cell depicts the entry of Ca^{2+} from the extracellular space (ECS) to the cytosol via TRPC1 channels, which replenishes the ER store.

5. Conclusions

The intent of this overview is to put forward the findings supporting the existence of various Ca^{2+} sources that mediate exocytotic release of the gliotrasmitter glutamate from astrocytes (Fig. 4). The existence of multiple Ca^{2+} delivery pathways has an intrinsic plastic potential, which may determine the kinetic parameters of gliotransmission. Indeed, Ca^{2+} signals originating from the ER could initiate relatively slow and sustained exocytosis, compatible with local endocrine action of gliotransmitters. In contrast, Ca^{2+} microdomains generated by Ca^{2+} entry through plasmalemmal channels/exchangers could create short-lived $[Ca^{2+}]_i$ microdomains that in turn would trigger fast local exocytosis. Thus, astrocytes could

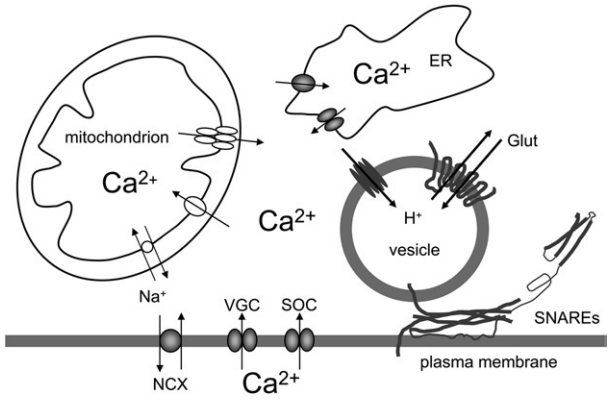

Fig. 4. Sources of Ca^{2+} for intracellular Ca^{2+} increase in Ca^{2+}-dependent exocytotic glutamate release from astrocytes. The accumulation of Ca^{2+} in cytosol could be caused by the entry of Ca^{2+} from the extracellular space via voltage-gated channels (VGC), store-operated channels (SOC) and the plasma membrane Na^+/Ca^{2+} exchanger (NCX). Cytosolic Ca^{2+} levels are modulated by the mitochondria that can take up Ca^{2+} via the Ca^{2+} uniporter during the cytosolic Ca^{2+} increase. As cytosolic Ca^{2+} declines due to extruding mechanisms, most notably the SERCA of the ER store, Ca^{2+} is slowly released by mitochondria into cytosol via the mitochondrial Na^+/Ca^{2+} exchanger as well as by the formation of the mitochondrial permeability transition pore. The predominant source of Ca^{2+} is available from the ER internal store that possess ryanodine and $InsP_3$ channels acting as conduits for Ca^{2+} delivery to the cytosol. The increase in cytosolic Ca^{2+} levels is sufficient and necessary to cause the fusion of glutamatergic vesicles to the plasma membrane and exocytotic release of glutamate. This process requires action by SNARE proteins. Vesicles are filled by glutamate (Glut) through the activity of vesicular glutamate transporters which use the proton gradient generated by the vacuolar type H^+-ATPase. Drawing is not to scale.

regulate the mode of the gliotransmitter release by employing different Ca^{2+} delivery pathways.

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